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Two Sibs With Partial Trisomy 2q

A.J. Barnicoat,[1]* I. Abusaad,[1] C.M. Mackie,[1] and M.F. Robards[2]

[1]*Department of Medical and Molecular Genetics, United Medical and Dental School, Guy's Hospital, London, United Kingdom*

[2]*Department of Paediatrics, Pembury Hospital, Pembury, Tunbridge Wells, United Kingdom*

We report on two sibs with facial anomalies and developmental delay. Partial trisomy 2q was detected only after parental chromosome studies showed the father to carry a balanced interchromosomal insertion of 2 (q24.3–q32.1) into 5q. Am. J. Med. Genet. 70:166–170, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: chromosome 2; trisomy 2q; interchromosomal insertion; aneuploidy syndrome

INTRODUCTION

We report on a brother and sister with similar facial anomalies and developmental delay born to nonconsanguineous parents. The children are trisomic for 2 (q24.3–q32.1), their father carrying a balanced interchromosomal insertion of this part of 2q into 5q.

CLINICAL REPORT

L.B., a boy, and K.B., a girl, are the only offspring of healthy nonconsaguineous Caucasian parents. At the time of L.B.'s birth, the father was 27 and the mother 20 years old; K.B. was born a year later. Subsequently, the mother had a third pregnancy with a new partner, which ended in spontaneous first trimester miscarriage. Twin paternal uncles of the children had cleft lip and palate repairs in childhood. There was no exposure to known teratogens during either pregnancy, both of which were uncomplicated. L.B. weighed 4.25 kg and K.B. 4.00 kg at term.

L.B. required a right inguinal hernia repair at age 7 months. He was first noted to be developmentally delayed at 2½ years when he was acquiring his first words. Glue ear was diagnosed, but the insertion of grommets did not substantially alter his language skills. There was minor delay in other areas of development, but the delay in speech and language was disproportionate. K.B. has followed a similar developmental course, although her problems were marginally less severe than those of her brother. Both children are in mainstream education, although additional classroom help is needed for L.B. Neither of the children have had major behavioural problems.

Both children have height, weight, and occipitofrontal circumferences between 10th and 50th centiles. General physical examination is normal apart from the following findings in both children: prominent forehead, hypertelorism, epicanthic folds, upslanting palpebral fissures, broad nasal bridge with a pinched tip and anteverted nares, long flat philtrum with thin upper vermilion border, brachycephaly, carious teeth, creased ear lobes, bilateral clinodactyly and camptodactyly of the fifth fingers, and mild pectus excavatum. K.B. also has had an intermittent convergent squint and a sacral pit. L.B. has a single palmar crease unilaterally and a small depigmented patch on the right side of the abdomen. (Figs. 1–3).

CYTOGENETICS

Chromosome studies were performed from peripheral blood obtained from the two sibs, using standard cytogenetic procedures. Some cultures were treated with ethidium bromide [Ikeuchi, 1984] or with methotrexate [Yunis, 1976] to obtain prometaphases.

By G-banding, an elongation of the long arm of chromosome 5 was noted in the two sibs, as a result of an unbalanced product of an interchromosomal insertion of chromosome 2 long arm (q24.3q32.1) into the chromosome 5 long arm at two possible insertion points depending on the orientation of the inserted segment (5q22.3 or 5q22.1). The chromosomes of both children show a der (5) inv ins (5;2) (q22.3;q32.1q24.3) or der (5) dir ins (5;2) (q22.1;q24.3q32.1). The father carries the same elongated chromosome 5 as his children, but also a deleted chromosome 2 as a result of a balanced interstitial deletion of the long arm of chromosome 2 and subsequent insertion into the long arm of chromosome 5 (Fig. 4). This karyotype is designated 46,XY,inv ins (5;2) (q22.3;q32.1q24.3) or dir ins (5;2) (q22.1;q24.3q32.1). The mother has a normal 46,XX karyotype.

Fluorescence in situ hybridisation (FISH) was carried out using whole chromosome paints (Cambio) labelled with either Biotin or FITC. Probes were denatured at 65°C for 10 minutes, and slides of fixed chro-

*Correspondence to: Dr. A.J. Barnicoat, who is now at Mothercare Department of Clinical Genetics and Fetal Medicine, Great Ormond Street Hospitals for Children NHS Trust, 30 Guilford Street, London WC1N 1EH, UK.

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Fig. 1. **a** and **b**: Frontal and side view of L.B.

Fig. 2. **a** and **b**: Frontal and side view of K.B.

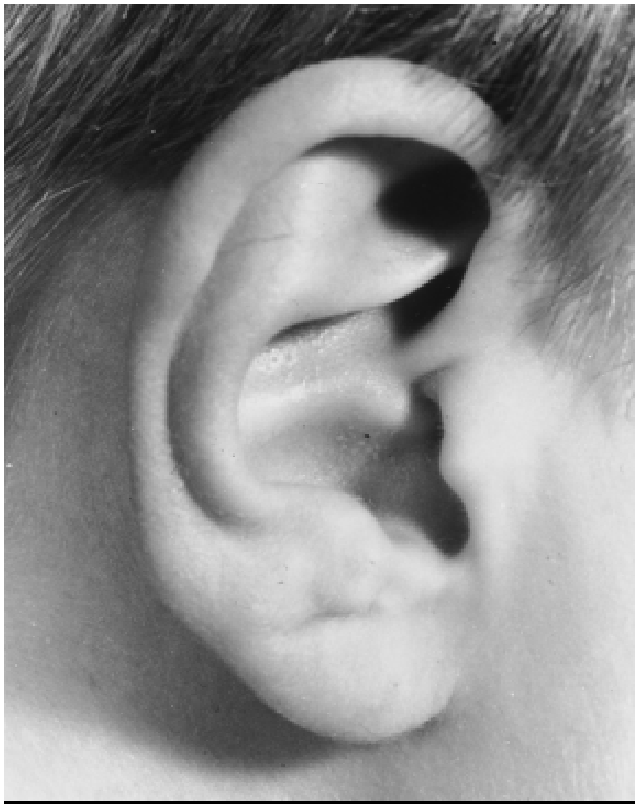

Fig. 3. Ear lobe creases of L.B.

mosome preparations were denatured in 70% deionised formamide/2 xSSC (pH 7.0) at 70°C for 2 minutes. Hybridisation took place overnight at 42°C in a humidified chamber. Slides were then washed twice in 50% formamide/2 × SSC (pH 7.0) at 42°C for 5 minutes followed by two washes in 2 × SSC at 42°C for 5 minutes. Biotinylated probes were detected with Texas Red (or FITC) Avidin DCS (Vector Labs), followed by amplification using biotinylated anti-Avidin (Vector Labs), then a second layer of Texas Red (or FITC) Avidin. FITC-labelled probes were detected with anti-FITC (Cambio) followed by FITC-anti-anti-FITC (Cambio). These two detection protocols were run concurrently when two-colour probing was carried out.

Signals were detected with an Axioplan fluorescence microscope, and images were produced using a cooled CCD camera equipped with Smartcapture Software (Digital Scientific) (Fig. 5).

DISCUSSION

These sibs, born to normal parents, have a very similar constellation of facial anomalies and developmental problems due to their partial trisomy 2q. Many previous reports of partial trisomy 2q have resulted from unbalanced products of reciprocal translocations and have therefore been trisomic for the whole of the terminal part of 2q, often accompanied by monosomy elsewhere. Similar but not identical isolated partial trisomy of 2q has been reported, in some cases associated with major internal manifestations as well as physical anomalies and developmental problems. A distinctive facial phenotype associated with partial trisomy 2q is apparent in these cases as in previous reports.

Couturier et al. [1977] found a boy with severe mental retardation, short stature, genital hypoplasia, kyphoscoliosis, and talipes to have a trisomy of 2 (q24–34), resulting from a maternal interstitial insertion in 6p. He had midface hypoplasia, hypertelorism, and epicanthic folds with a large mouth. His fingers were short with hypoplastic nails.

A female infant reported by Schumacher et al. [1983]

TABLE I. Previous Reports of Partial Trisomy 2q*

Finding	1	2	3	4	5	6
Trisomy 2q	33–37	21–33	24.2–31.05	21–31	24–34	24.3–32.1
Developmental delay	+	?	+	?	+	+
Prominent forehead	+	+	+	+	+	+
Hypertelorism	–	–	+	?	+	+
Upslanting palpebral fissures	+	+	+	+	+	+
Depressed nasal bridge	+	+	+	+	+	+
Anteverted nostrils	+	+	+	+	+	+
Long philtrum	+	+	+	?	?	+
Ear abnormalities	+	+	+	+	–	+
Small nails	+	+	?	?	+	–
Cardiac abnormality	–	+	–	–	–	–
Renal abnormality	–	+	–	+	–	–
Genital abnormality	+	+	–	+	+	–

*1. Dennis et al. [1978]; 2. Schumacher et al. [1983]; 3. Moller et al. [1984]; 4. Marchese et al. [1984]; 5. Couturier et al. [1977]; 6. Cases reported here.

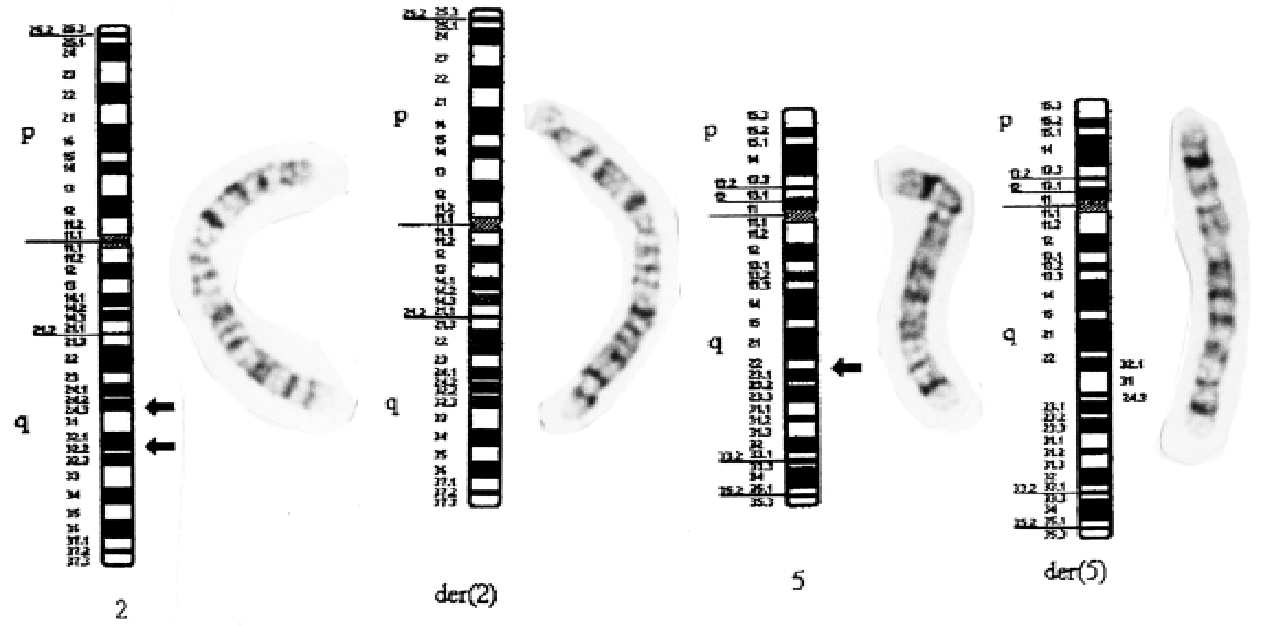

Fig. 4. Partial karyotype of GTG banded chromosomes from cultures of peripheral blood lymphocytes from the father of L.B. and K.B. Arrows indicate breakpoints on chromosome 2 and insertion of a small segment from the chromosome 2 long arm into chromosome 5 long arm.

died in the neonatal period. She had a de novo duplication of 2 (q21–q33). The birth weight was below 3rd centile. Autopsy showed that she had complex congenital heart disease and small, abnormally fissured lungs. A four-lobed horseshoe kidney with renal dysplasia and atresia of the ureter on the right was found with a bicornuate uterus and atretic vagina. There were accessory spleens. Facial anomalies included a depressed nasal bridge and short nose with anteverted nares, a long philtrum, and prominent forehead with malformed ears. Small toenails were observed.

A female fetus terminated because of a de novo dup (2) (q21–31) was shown to have a horseshoe kidney and hypoplastic external genitalia. Facial anomalies in-

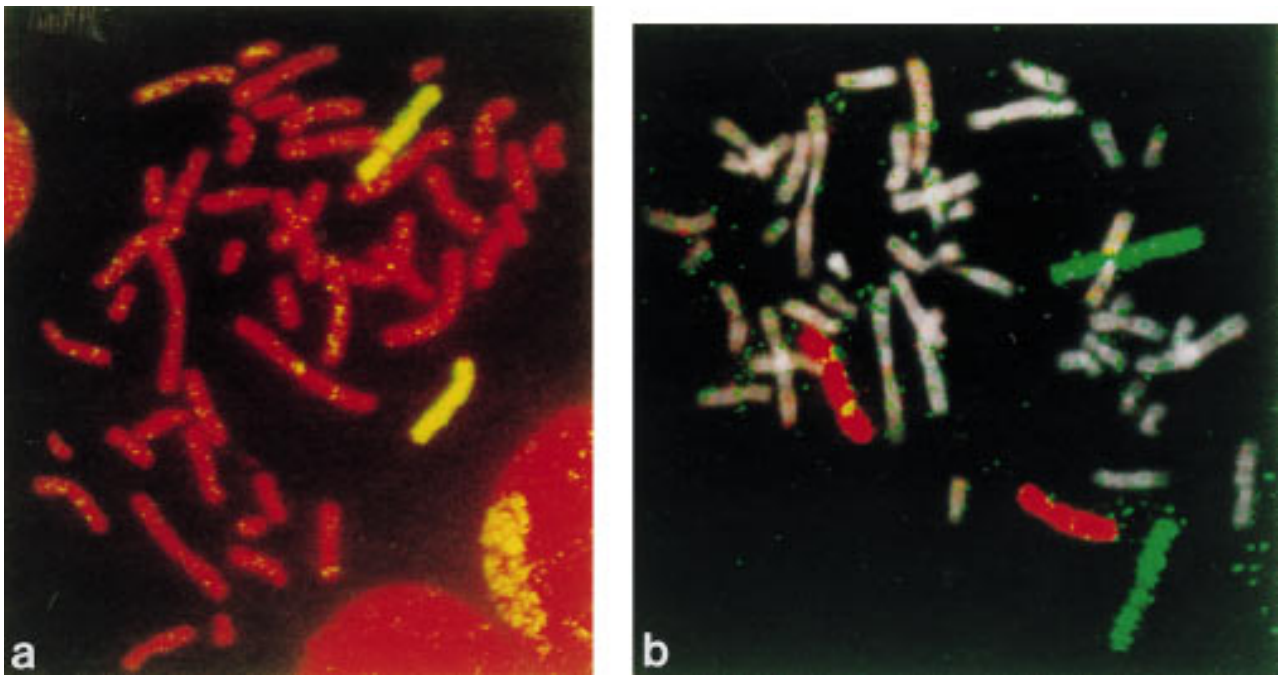

Fig. 5. **a:**Biotinylated whole chromosome paint specific for chromosome 5 hybridised to metaphase chromosomes from the father of L.B. and K.B. and detected using FITC Avidin. Chromosomes were counterstained with propidium iodide. One homologue shows a region with no signal, corresponding to the inserted material observed in G-banded preparations.

cluded low set floppy ears, a prominent forehead, flattened nose with anteverted nostrils, upslanting palpebral fissures, a large mouth, and micrognathia [Marchese et al., 1984].

The boy reported by Dennis et al. [1978] has some similar facial findings, but the portion of 2q he was trisomic for appears to be distal to that seen in the cases presented here, unless the breakpoints reported are inaccurate.

A large family segregating an inv ins (7;2) (q21.2;q31.05q24.2) segregating had members with 2q trisomy [Moller et al., 1984]. The two trisomic individuals were moderately mentally retarded and did not have apparent internal malformations. They had prominent forehead, hypertelorism, upslanting palpebral fissures, flat nasal bridge with midface hypoplasia and upturned nostrils, micrognathia, low set malformed ears, and clinodactyly of the fifth fingers.

The findings in these cases are compared in Table I. The facial anomalies are similar, but the cases reported here, like the cases of Moller et al. [1984], lack major internal malformations. There appears to be some relationship between the extent of the trisomic region and the severity of the clinical manifestations, with the cases trisomic for a more extensive part of 2q being associated with internal malformations. Few disease genes have been mapped to this part of 2q, although the gene for type III collagen is located in this part of 2q [Emanuel et al., 1985; Tiller et al., 1994]. Mutations in this gene are associated with Ehlers-Danlos syndrome type IV [Nuytinck et al., 1994]. No features suggestive of this condition were seen in these sibs.

The ear lobe creases seen in the sibs described here are novel in reports of trisomy 2q. Ear lobe creases are recognised in conditions such as Wiedemann-Beckwith syndrome, Simpson-Golabi-Behmel syndrome, the recessive condition described by Gurrieri et al. [1992], and the family reported by Méhes [1991]. The facial gestalt in these sibs was a suggestive of William's syndrome, although the children lacked the characteristic behavioural phenotype of this condition.

The findings in this pair of sibs confirm the phenotype of a partial 2q duplication syndrome and emphasise the importance of parental chromosome studies in cases of familial multiple abnormalities that do not fit a recognised syndrome.

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